DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

NDA 19-157/S-011, S-012, S-013, S-015
Medeva Phamaceuticals **DEC 1 7 1998**
Attention: Robert B. Parker, Ph.D.
Senior Director, Regulatory Affairs
755 Jefferson Road
Post Office Box 1710
Rochester, New York 14603

Dear Dr. Parker:

Please refer to your supplemental new drug applications dated August 11, 1994 and received August 15, 1994, (S-011); September 9, 1994 and received September 14, 1994, (S-012); March 15, 1996 and received March 20, 1996, (S-013); and June 18, 1998, received June 23, 1998, (S-015) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Pediapred (prednisolone sodium phosphate, USP) Oral Solution.

We acknowledge receipt of your submissions dated and September 24, 1998.

These supplemental new drug applications provide for the use of Pediapred Oral Solution for Pediatric Use (S-015), updated information in the CLINICAL PHARMACOLOGY section (S012), and changes being affected to the WARNINGS section (5-011, S-013).

Please note that as a result of the Agency's effort to update labeling for all systemic glucocorticoids, various sections of the labeling has been revised and reformatted.

We have completed the review of these supplemental applications, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the enclosed labeling text. Accordingly, these supplemental applications are approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert). Marketing the products with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed to each application. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, these submissions should be designated "FPL for approved supplement NDA 19-157/5-011, S-012, S-013, S-015." Approval of these submissions by FDA is not required before the labeling is used.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MED WATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, contact Sharon Schmidt, M.S., Project Manager, at (301) 827-2536.

Sincerely,

John E. Hyde, Ph.D., M.D.
Acting Deputy Director
Division of Anti-Inflammatory, Analgesic and Ophthalmic Drug Products, HFE-550
Office of Drug Evaluation V
Center for Drug Evaluation and Research

Enclosure

DEC 17 1998

PEDIAPRED® ORAL SOLUTION
(prednisolone sodium phosphate, USP)

DESCRIPTION:
PEDIAPRED® (prednisolone sodium phosphate, USP) Oral Solution is a dye free, colorless to light straw colored, raspberry flavored solution. Each 5 mL (teaspoonful) of PEDIAPRED contains 6.7 mg prednisolone sodium phosphate (5 mg prednisolone base) in a palatable, aqueous vehicle.

Pediapred also contains dibasic sodium phosphate, edetate disodium, methylparaben, purified water, sodium biphosphate, sorbitol, natural and artificial raspberry flavor.

Prednisolone sodium phosphate occurs as white or slightly yellow, friable granules or powder. It is freely soluble in water; soluble in methanol; slightly soluble in alcohol and in chloroform; and very slightly soluble in acetone and in dioxane. The chemical name of prednisolone sodium phosphate is pregna- 1,4-diene-3 ,20-dione, 11,1 7-dihydroxy-2 1-(phosphonooxy)-,disodium salt,(11ß)-. The empirical formula is $C_{21}H_{27}Na_2O_8P$; the molecular weight is 484.39. Its chemical structure is:

[structure]

Pharmacological Category: Glucocorticoid

CLINICAL PHARMACOLOGY:
Naturally occurring glucocorticoids (hydrocortisone), which also have salt-retaining properties, are used as replacement therapy in adrenocortical deficiency states. Their synthetic analogs are primarily used for their potent anti-inflammatory effects in disorders of many organ systems.

Prednisolone is a synthetic adrenocortical steroid drug with predominantly glucocorticoid properties. Some of these properties reproduce the physiological actions of endogenous glucocorticosteroids, but others do not necessarily reflect any of the adrenal hormones' normal functions; they are seen only after administration of large therapeutic doses of the drug. The pharmacological effects of prednisolone which are due to its glucocorticoid properties include: promotion of gluconeogenesis; increased deposition of glycogen in the liver; inhibition of the utilization of glucose; anti-insulin activity; increased

catabolism of protein; increased lipolysis; stimulation of fat synthesis and storage; increased glomerular filtration rate and resulting increase in urinary excretion of urate (creatinine excretion remains unchanged); and increased calcium excretion.

Depressed production of eosinophils and lymphocytes occurs, but erythropoiesis and production of polymorphonuclear leukocytes are stimulated. Inflammatory processes (edema, fibrin deposition, capillary dilatation, migration of leukocytes and phagocytosis) and the later stages of wound healing (capillary proliferation, deposition of collagen, cicatrization) are inhibited.

Prednisolone can stimulate secretion of various components of gastric juice. Suppression of the production of corticotropin may lead to suppression of endogenous corticosteroids. Prednisolone has slight mineralocorticoid activity, whereby entry of sodium into cells and loss of intracellular potassium is stimulated. This is particularly evident in the kidney, where rapid ion exchange leads to sodium retention and hypertension.

Prednisolone is rapidly and well absorbed from the gastrointestinal tract following oral administration. PEDIAPRED Oral Solution produces a 14% higher peak plasma level of prednisolone which occurs 20% faster than that seen with tablets. Prednisolone is 70-90% protein-bound in the plasma and it is eliminated from the plasma with a half-life of 2 to 4 hours. It is metabolized mainly in the liver and excreted in the urine as sulfate and glucuronide conjugates.

INDICATIONS AND USAGE:
PEDIAPRED Oral Solution is indicated in the following conditions:

1. **Endocrine Disorders**
   Primary or secondary adrenocortical insufficiency (hydrocortisone or cortisone is the first choice; synthetic analogs may be used in conjunction with mineralocorticoids where applicable; in infancy mineralocorticoid supplementation is of particular importance); congenital adrenal hyperplasia; hypercalcemia associated with cancer; nonsuppurative thyroiditis.

2. **Rheumatic Disorders**
   As adjunctive therapy for short term administration (to tide the patient over an acute episode or exacerbation) in: psoriatic arthritis; rheumatoid arthritis, including juvenile rheumatoid arthritis (selected cases may require low dose maintenance therapy); ankylosing spondylitis; acute and subacute bursitis; acute nonspecific tenosynovitis; acute gouty arthritis; epicondylitis. For the treatment of systemic lupus erythematosus, dermatomyositis (polymyositis), polymyalgia rheumatica, Sjogren’s syndrome, relapsing polychondritis, and certain cases of vasculitis.

3. **Dermatologic Diseases**

Pemphigus; bullous dermatitis herpetiformis; severe erythema multiforme (Stevens-Johnson syndrome); exfoliative erythroderma; mycosis fungoides;

4. **Allergic State**s

Control of severe or incapacitating allergic conditions intractable to adequate trials of conventional treatment in adult and pediatric populations with: seasonal or perennial allergic rhinitis; asthma; contact dermatitis, atopic dermatitis, serum sickness; drug hypersensitivity reactions.

5. **Ophthalmic Disease**s

Uveitis and ocular inflammatory conditions unresponsive to topical corticosteroids; temporal arteritis; sympathetic ophthalmia.

6. **Respiratory Diseases**

Symptomatic sarcoidosis; idiopathic eosinophilic pneumonias; fulminating or disseminated pulmonary tuberculosis when used concurrently with appropriate antituberculous chemotherapy; asthma (as distinct from allergic asthma listed above under “Allergic States”), hypersensitivity pneumonitis, idiopathic pulmonary fibrosis, acute exacerbations of chronic obstructive pulmonary disease (COPD), and Pneumocystis carinii pneumonia (PCP) associated with hypoxemia occurring in an HIV (+) individual who is also under treatment with appropriate anti-PCP antibiotics. Studies support the efficacy of systemic corticosteroids for the treatment of these conditions: allergic bronchopulmonary aspergillosis, idiopathic bronchiolitis obliterans with organizing pneumonia.

7. **Hematologic Disorders**

Idiopathic thrombocytopenic purpura in adults; selected cases of secondary thrombocytopenia; acquired (autoimmune) hemolytic anemia; pure red cell aplasia; Diamond-Blackfan anemia.

8. **Neoplastic Diseases**

For the treatment of acute leukemia and aggressive lymphomas in adults and children.

9. **Edematous States**
To induce diuresis or remission of proteinuria in nephrotic syndrome in adults with lupus erythematosus and in adults and pediatric populations, with idiopathic nephrotic syndrome, without uremia.

10. **Gastrointestinal Diseases**
To tide the patient over a critical period of the disease in: ulcerative colitis; regional enteritis.

11. **Nervous System**
Acute exacerbations of multiple sclerosis.

12. **Miscellaneous**
Tuberculous meningitis with subarachnoid block or impending block, tuberculosis with enlarged mediastinal lymph nodes causing respiratory difficulty, and tuberculosis with pleural or pericardial effusion (appropriate antituberculous chemotherapy must be used concurrently when treating any tuberculosis complications); Trichinosis with neurologic or myocardial involvement; acute or chronic solid organ rejection (with or without other agents).

CONTRAINDICATIONS:
Systemic fungal infections.
Hypersensitivity to the drug or any of its components.

WARNINGS:
General:
In patients on corticosteroid therapy subjected to unusual stress, increased dosage of rapidly acting corticosteroids before, during and after the stressful situation is indicated.

Endocrine:
Corticosteroids can produce reversible hypothalamic-pituitary adrenal (HPA) axis suppression with the potential for glucocorticosteroid insufficiency after withdrawal of treatment.

Metabolic clearance of corticosteroids is decreased in hypothyroid patients and increased in hyperthyroid patients. Changes in thyroid status of the patient may necessitate adjustment in dosage.

Infections (general):
Persons who are on drugs which suppress the immune system are more susceptible to infections than healthy individuals. There may be decreased resistance and inability to localize infection when corticosteroids are used. Infection with any pathogen including viral, bacterial, fungal, protozoan or helminthic infection, in any location of the body, may be associated with the use of corticosteroids alone or in combination with other immunosuppressive agents that affect humoral or cellular immunity, or neutrophil function. These infections may be mild to severe, and, with increasing doses of corticosteroids, the rate of occurance of infectious complications increases. Corticosteriods may also mask some signs of infection after it has already started.

Viral infections:
Chicken pox and measles, for example, can have a more serious or even fatal course in non-immune children or adults on corticosteroids. In such children or adults who have not had these diseases, particular care should be taken to avoid exposure. How the dose, route and duration of corticosteroid administration affect the risk of developing a disseminated infection is not known. The contribution of the underlying disease andlor prior corticosteroid treatment to the risk is also not known. If exposed to chicken pox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If exposed to measles, prophylaxis with immunoglobulin (IG) may be indicated. (See the respective package inserts for complete VZIG and IG prescribing information). If chicken pox develops, treatment with antiviral agents should be considered.

Special pathogens:
Latent disease may be activated or there may be an exacerbation of intercurrent infections due to pathogens, including those caused by Candida, Mycobacterium, Ameba, Toxoplasma, Pneumocystis, Cryptococus, Nocardia, etc.

Corticosteriods may activate latent amebiasis. Therefore, it is recommended that latent or active amebiasis be ruled out before initiating corticosteroid therapy in any patient who has spent time in the tropics or in any patient with unexplained diarrhea.

Similarly, corticosteroids should be used with great care in patients with known or suspected Strongyloides (threadworm) infestation. In such patients, corticosteroid-induced immunosuppression may lead to Strongyloides hyperinfection and dissemination with widespread larval migration, often accompanied by severe enterocolitis and potentially fatal gram-negative septicemia.

Corticosteroids should not be used in cerebral malaria.

Tuberculosis:
The use of prednisolone in active tuberculosis should be restricted to those cases of fulminating or disseminated tuberculosis in which the corticosteroid is used for the management of the disease in conjunction with an appropriate antituberculous regimen.

If corticosteroids are indicated in patients with latent tuberculosis or tuberculin reactivity, close observation is necessary as reactivation of the disease may occur. During prolonged corticosteroid therapy these patients should receive chemoprophylaxis.

Vaccination:
Administration of live or live, attenuated vaccines is contraindicated in patients receiving immunosuppressive doses of corticosteroids. Killed or inactivated vaccines may be administered, however, the response to such vaccines can not be predicted. Immunization procedures may be undertaken in patients who are receiving corticosteroids as replacement therapy, e.g., for Addison's disease.

Ophthalmic:
Use of corticosteroids may produce posterior subcapsular cataracts, glaucoma with possible damage to the optic nerves, and may enhance the establishment of secondary ocular infections due to bacteria, fungi or viruses. The use of oral corticosteroids is not recommended in the treatment of optic neuritis and may lead to an increase in the risk of new episodes. Corticosteroids should not be used in active ocular herpes simplex.

Cardio-renal:
Average and large doses of hydrocortisone or cortisone can cause elevation of blood pressure, salt and water retention, and increased excretion of potassium. These effects are less likely to occur with the synthetic derivatives except when used in large doses. Dietary salt restriction and potassium supplementation may be necessary. All corticosteroids increase calcium excretion.

PRECAUTIONS:
General:
The lowest possible dose of corticosteroid should be used to control the condition under treatment, and when reduction in dosage is possible, the reduction should be gradual.

Since complications of treatment with glucocorticoids are dependent on the size of the dose and the duration of treatment, a risk/benefit decision must be made in each individual case as to dose and duration of treatment and as to whether daily or intermittent therapy should be used.

There is an enhanced effect of corticosteroids in patients with hypothyroidism and in those with cirrhosis.

Kaposi’s sarcoma has been reported to occur in patients receiving corticosteroid therapy, most often for chronic conditions. Discontinuation of corticosteroids may result in clinical improvement.

Endocrine:
Drug-induced secondary adrenocortical insufficiency may be minimized by gradual reduction of dosage. This type of relative insufficiency may persist for months after discontinuation of therapy; therefore, in any situation of stress occurring during that period, hormone therapy should be reinstituted. Since mineralocorticoid secretion may be impaired, salt and/or a mineralocorticoid should be administered concurrently.

Ophthalmic:
Intraocular pressure may become elevated in some individuals. If steroid therapy is continued for more than 6 weeks, intraocular pressure should be monitored.

Neuro-psychiatric:
Although controlled clinical trials have shown corticosteroids to be effective in speeding the resolution of acute exacerbations of multiple sclerosis, they do not show that they affect the ultimate outcome or natural history of the disease. The studies do show that relatively high doses of corticosteroids are necessary to demonstrate a significant effect.
(See DOSAGE AND ADMINISTRATION.)

An acute myopathy has been observed with the use of high doses of corticosteroids, most often occurring in patients with disorders of neuromuscular transmission (e.g., myasthenia gravis), or in patients receiving concomitant therapy with neuromuscular blocking drugs (e.g., pancuronium). This acute myopathy is generalized, may involve ocular and respiratory muscles, and may result in quadriparesis. Elevation of creatinine kinase may occur. Clinical improvement or recovery after stopping corticosteroids may require weeks to years.

Psychic derangements may appear when corticosteroids are used, ranging from euphoria, insomnia, mood swings, personality changes, and severe depression, to frank psychotic manifestations. Also, existing emotional instability or psychotic tendencies may be aggravated by corticosteroids.

Gastrointestinal:
Steroids should be used with caution in nonspecific ulcerative colitis, if there is a probability of impending perforation, abscess or other pyogenic infection; diverticulitis; fresh intestinal anastomoses; active or latent peptic ulcer.

Signs of peritoneal irritation following gastrointestinal perforation in patients receiving corticosteroids may be minimal or absent.

Cardio-renal:
As sodium retention with resultant edema and potassium loss may occur in patients receiving corticosteroids, these agents should be used with caution in patients with hypertension, congestive heart failure, or renal insufficiency.

Musculoskeletal:
Corticosteroids decrease bone formation and increase bone resorption both through their effect on calcium regulation (i.e. decreasing absorption and increasing excretion) and inhibition of osteoblast function. This, together with a decrease in the protein matrix of the bone secondary to an increase in protein catabolism,and reduced sex hormone production, may lead to inhibition of bone growth in children and adolescents and the development of osteoporosis at any age. Special consideration should be given to patients at increased risk of osteoporosis (i.e., postmenopausal women) before initiating corticosteroid therapy.

Information for Patients:
Patients should be warned not to discontinue the use of PEDIAPRED abruptly or without medical supervision, to advise any medical attendants that they are taking PEDIAPRED and to seek medical advice at once should they develop fever or other signs of infection.

Persons who are on immunosuppressant doses of corticosteroids should be warned to avoid exposure to chicken pox or measles. Patients should also be advised that if they are exposed, medical advice should be sought without delay.

Drug Interactions:
Drugs such as barbiturates, phenytoin, ephedrine, and rifampin, which induce hepatic microsomal drug metabolizing enzyme activity may enhance metabolism of prednisolone and require that the dosage of PEDIAPRED be increased.

Increased activity of both cyclosporin and corticosteroids may occur when the two are used concurrently. Convulsions have been reported with this concurrent use.

Estrogens may decrease the hepatic metabolism of certain corticosteroids thereby increasing their effect.

Ketoconazole have been reported to decrease the metabolism of certain corticosteroids by up to 60% leading to an increased risk of corticosteroid side effects.

Coadministration of corticosteroids and warfarin usually results in inhibition of response to warfarin, although there have been some conflicting reports. Therefore, coagulation indices should be monitored frequently to maintain the desired anticoagulant effect.

Concomitant use of aspirin (or other non-steroidal anti-inflammatory agents) and corticosteroids increases the risk of gastrointestinal side effects. Aspirin should be used cautiously in conjunction with corticosteroids in hypoprothrombinemia. The clearance of salicylates may be increased with concurrent use of corticosteroids.

When corticosteroids are administered concomitantly with potassium-depleting agents (i.e., diuretics, amphotericin-B), patients should be observed closely for development of hypokalemia. Patients on digitalis glycosides may be at increased risk of arrhythmias due to hypokalemia.

Concomitant use of anticholinesterase agents and corticosteroids may produce severe weakness in patients with myasthenia gravis. If possible, anicholinesterase agents should be withdrawn at least 24 hours before initiating corticosteroid therapy.

Due to inhibition of antibody response, patients on prolonged corticosteroid therapy may exhibit a diminished response to toxoids and live or inactivated vaccines. Corticosteroids may also potentiate the replication of some organisms contained in live attenuated vaccines. If possible, routine administration of vaccines or toxoids should be deferred until corticosteroid therapy is discontinued.

Because corticosteroids may increase blood glucose concentrations, dosage adjustments of antidiabetic agents may be required.

Corticosteroids may suppress reactions to skin tests.

Pregnancy: Teratogenic effects: Pregnancy Category C.
Prednisolone has been shown to be teratogenic in many species when given in doses equivalent to the human dose. Animal studies in which prednisolone has been given to pregnant mice, rats, and rabbits have yielded an increased incidence of cleft palate in the offspring. There are no adequate and well-controlled studies in pregnant women. PEDIAPRED should be used during pregnancy only if the potential benefit justifies the

potential risk to the fetus. Infants born to mothers who have received corticosteroids during pregnancy should be carefully observed for signs of hypoadrenalism.

Nursing Mothers:
Systemically administered corticosteroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. Caution should be exercised when PEDIAPRED is administered to a nursing woman.

Pediatric Use:
The efficacy and safety of prednisolone in the pediatric population are based on the well-established course of effect of corticosteroids which is similar in pediatric and adult populations. Published studies provide evidence of efficacy and safety in pediatric patients for the treatment of nephrotic syndrome (>2 years of age), and aggressive lymphomas and leukemias (>1 month of age). However, some of these conclusions and other indications for pediatric use of corticosteroid, e.g., severe asthma and wheezing, are based on adequate and well-controlled trials conducted in adults, on the premises that the course of the diseases and their pathophysiology are considered to be substantially similar in both populations.

The adverse effects of prednisolone in pediatric patients are similar to those in adults (see ADVERSE REACTIONS). Like adults, pediatric patients should be carefully observed with frequent measurements of blood pressure, weight, height, intraocular pressure, and clinical evaluation for the presence of infection, psychosocial disturbances, thromboembolism, peptic ulcers, cataracts, and osteoporosis. Children who are treated with corticosteroids by any route, including systemically administered corticosteroids, may experience a decrease in their growth velocity. This negative impact of corticosteroids on growth has been observed at low systemic doses and in the absence of laboratory evidence of HPA axis suppression (i.e., cosyntropin stimulation and basal cortisol plasma levels). Growth velocity may therefore be a more sensitive indicator of systemic corticosteroid exposure in children than some commonly used tests of HPA axis function. The linear growth of children treated with corticosteroids by any route should be monitored, and the potential growth effects of prolonged treatment should be weighed against clinical benefits obtained and the availability of other treatment alternatives. In order to minimize the potential growth effects of corticosteroids, children should be titrated to the lowest effective dose.

ADVERSE REACTIONS (listed alphabetically under each subsection):
Fluid and Electrolyte Disturbances: Congestive heart failure in susceptible patients; fluid retention; hypertension; hypokalemic alkalosis; potassium loss; sodium retention;

Cardiovascular: Hypertrophic cardiomyopathy in premature infants.

Musculoskeletal: Aseptic necrosis of femoral and humeral heads; loss of muscle mass; muscle weakness; osteoporosis; pathologic fracture of long bones; steroid myopathy; tendon rupture; vertebral compression fractures.

Gastrointestinal: Abdominal distention; elevation in serum liver enzyme levels (usually reversible upon discontinuation); pancreatitis; peptic ulcer with possible perforation and hemorrhage; ulcerative esophagitis.

Dermatologic: Facial erythema; increased sweating; impaired wound healing; may suppress reactions to skin tests; petechiae and ecchymoses; thin fragile skin; urticaria; edema.

Metabolic: Negative nitrogen balance due to protein catabolism.

Neurological: Convulsions; headache; increased intracranial pressure with papilledema (pseudotumor cerebri), usually following discontinuation of treatment; psychic disorders; vertigo.

Endocrine: Decreased carbohydrate tolerance; development of cushingoid state; hirsutism; increased requirements for insulin or oral hypoglycemic agents in diabetes; manifestations of latent diabetes mellitus; menstrual irregularities; secondary adrenocortical and pituitary unresponsiveness, particularly in times of stress, as in trauma, surgery or illness; suppression of growth in children.

Ophthalmic: Exophthalmos; glaucoma; increased intraocular pressure; posterior subcapsular cataracts.

Other: Increased appetite; malaise; nausea; weight gain.

OVERDOSAGE:
The effects of accidental ingestion of large quantities of prednisolone over a very short period of time have not been reported, but prolonged use of the drug can produce mental symptoms, moon face, abnormal fat deposits, fluid retention, excessive appetite, weight gain, hypertrichosis, acne, striae, ecchymosis, increased sweating, pigmentation, dry scaly skin, thinning scalp hair, increased blood pressure, tachycardia, thrombophlebitis, decreased resistance to infection, negative nitrogen balance with delayed bone and wound healing, headache, weakness, menstrual disorders, accentuated menopausal symptoms, neuropathy, fractures, osteoporosis, peptic ulcer, decreased glucose tolerance, hypokalemia, and adrenal insufficiency. Hepatomegaly and abdominal distention have been observed in children.

Treatment of acute overdosage is by immediate gastric lavage or emesis followed by supportive and symptomatic therapy. For chronic overdosage in the face of severe disease requiring continuous steroid therapy the dosage of prednisolone may be reduced only temporarily, or alternate day treatment may be introduced.

DOSAGE AND ADMINISTRATION:
The initial dosage of PEDIAPRED may vary from 5 mL to 60 mL (5 to 60 mg prednisolone base) per day depending on the specific disease entity being treated. In situations of less severity, lower doses will generally suffice while in selected patients higher initial doses may be required. The initial dosage should be maintained or adjusted until a satisfactory response is noted. If after a reasonable period of time, there is a lack of satisfactory clinical response, PEDIAPRED should be discontinued and the patient placed on other appropriate therapy**. IT SHOULD BE EMPHASIZED THAT DOSAGE REQUIREMENTS ARE VARIABLE AND MUST BE INDIVIDUALIZED ON THE BASIS OF THE DISEASE UNDER TREATMENT AND THE RESPONSE OF THE PATIENT**. After a favorable response is noted, the proper maintenance dosage should be determined by decreasing the initial drug dosage in small decrements at appropriate time intervals until the lowest dosage which will maintain an adequate clinical response is reached. It should be kept in mind that constant monitoring is needed in regard to drug dosage. Included in the situations which may make dosage adjustments necessary are changes in clinical status secondary to remissions or exacerbations in the disease process, the patient's individual drug responsiveness, and the effect of patient exposure to stressful situations not directly related to the disease entity under treatment; in this latter situation it may be necessary to increase the dosage of PEDIAPRED for a period of time consistent with the patient's condition. If after long term therapy the drug is to be stopped, it is recommended that it be withdrawn gradually rather than abruptly.

In the treatment of acute exacerbations of multiple sclerosis, daily doses of 200 mg of prednisolone for a week followed by 80 mg every other day or 4 to 8 mg dexamethasone every other day for one month have been shown to be effective.

In pediatric patients, the initial dose of PEDIAPRED may vary depending on the specific disease entity being treated. The range of initial doses is 0.14 to 2 mg/kg/day in three or four divided doses (4 to 60 mg/m2bsa/day).

The standard regimen used to treat nephrotic syndrome in pediatric patients is 60 mg/m2/day given in three divided doses for 4 weeks, followed by 4 weeks of single dose alternate-day therapy at 40 mg/m2/day.

The National Heart, Lung, and Blood Institute (NHLBI) recommended dosing for systemic *prednisone, prednisolone or methylprednisolone* in children whose asthma is uncontrolled by inhaled corticosteroids and long-acting bronchodilators is 1-2 mg/kg/day in single or divided doses. It is further recommended that short course, or "burst" therapy, be continued until a child achieves a peak expiratory flow rate of 80% of his or her personal best or symptoms resolve. This usually requires 3 to 10 days of treatment, although it can take longer. There is no evidence that tapering the dose after improvement will prevent a relapse.

For the purpose of comparison, the following is the equivalent milligram dosage of the various glucocorticoids:

Cortisone, 25	*Triamcinolone, 4*
Hydrocortisone, 20	*Paramethasone, 2*
Prednisolone, 5	*Betamethasone, 0.75*
Prednisone, 5	*Dexamethasone, 0.75*
Methylprednisolone, 4	

These dose relationships apply only to oral or intravenous administration of these compounds. When these substances or their derivatives are injected intramuscularly or into joint spaces, their relative properties may be greatly altered.

HOW SUPPLIED:
PEDIAPRED (prednisolone sodium phosphate oral solution, USP) Oral Solution is a colorless to light straw colored solution containing 6.7 mg prednisolone sodium phosphate (5 mg prednisolone base) per 5 mL (teaspoonful).

NDC 53014-250-0 1 120 mL bottle

Store at 4°-25°C (39°-77°F). May be refrigerated. Keep tightly closed and out of the reach of children.

Rx only

Medeva Pharmaceuticals, Inc.
Rochester, NY 14623 USA

Rev. X/XX RXXXX